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Original Articles

Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler

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A new formulation of mometasone furoate (MF) for administration by dry powder inhaler (DPI) was evaluated for the treatment of asthma. A 12-week, double-blind, placebo-controlled dose-ranging study compared the efficacy and safety of three doses of MF DPI (100, 200 and 400 mcg b.i.d) with beclomethasone dipropionate (BDP) 168 mcg b.i.d. administered by metered dose inhaler in 365 adult or adolescent patients being treated with inhaled glucocorticoids. The mean change from baseline to endpoint (last treatment visit) for forced expiratory volume in 1 sec (FEV_1) was the primary efficacy variable. Secondary efficacy variables included other objective measures of pulmonary function [forced vital capacity (FVC), forced expiratory flow 25–75% ($FEV_{25-75\%}$) and peak expiratory flow rate (PEFR)] as well as subjective measures of therapeutic response (patients' daily evaluation of asthma symptoms and physicians' evaluation). At endpoint, all four active treatments were significantly more effective than placebo ($P<0{\cdot}01$) in improving FEV_1 (MF DPI 5 to 7%, BDP 3%, placebo −6·6%) and all other measures of pulmonary function (FVC: MF DPI 4 to 5%, BDP 2%, placebo −4·7%; $FEF_{25-75\%}$: MF DPI 6 to 18%, BDP 7·5%, placebo −9.5%; PEFR (AM): MF DPI 5 to 10%, BDP 5·7 %, placebo −7%). A consistent trend was observed for better improvement in patients treated with MF DPI 200 mcg b.i.d. than with MF DPI 100 mcg b.i.d., with no apparent additional benefit of MF DPI 400 mcg b.i.d. Results for the MF DPI 100 mcg b.i.d. and BDP 168 mcg b.i.d. treatment groups were similar. Patients' and physicians' subjective evaluations of

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symptoms found similar improvement in the MF DPI 200 and 400 mcg b.i.d. treatment groups, which were slightly better than that in the MF DPI 100 mcg b.i.d. group. Symptoms tended to worsen in the placebo group. MF DPI was well tolerated at all dose levels and the most frequently reported treatment-related adverse effects were headache, pharyngitis and oral candidiasis. No evidence of HPA-axis suppression was detected in any treatment group. In summary, all doses of MF DPI were well tolerated and significantly improved lung function and MF DPI 400 mcg (200 mcg b.i.d.) was the optimal dose in this study of patients with moderate persistent asthma.

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Introduction

Inhaled glucocorticoids are the most effective medication for the long-term control of mild, moderate or severe persistent asthma (1–3). Their potent anti-inflammatory activity is responsible for their therapeutic effects, which include control of asthma symptoms, improvement of pulmonary function, decrease in airway hyperresponsiveness and, possibly, prevention of airway wall remodeling (4).

Although inhaled glucocorticoids are generally safe and well-tolerated, systemic effects have been observed with currently available agents, particularly at high doses (4–6). Although the risk of systemic adverse effects with inhaled glucocorticoids is much lower than it is with their oral counterparts, the potential for systemic exposure is increased in patients who require long-term or high-dose inhaled glucocorticoids or who take concomitant glucocorticoid therapy for other conditions, such as allergic rhinitis. Thus, there is a therapeutic benefit from potent inhaled glucocorticoids with extremely low systemic bioavailability.

The efficacy of an inhaled glucocorticoid depends not only on the pharmacological activity of the drug molecule, but also on the ability of the inhaler device to deliver therapeutic doses to the sites of airway inflammation. Many of the currently available metered dose inhalers (MDIs) and dry powder inhalers (DPIs) demonstrate substantial variations in the proportion of the delivered dose that actually reaches the conducting airways (4). Thus, a need also exists for improved delivery systems as well as formulations that are free of chlorofluorocarbons, which are being phased out in all manufactured products because of environmental concerns.

Mometasone furoate (MF) is a highly potent topical glucocorticoid that has been shown to be effective in controlling the symptoms of seasonal and perennial rhinitis with once-daily administration as an aqueous nasal spray (MFNS) (7–9). Following intranasal administration, MF had negligible systemic bioavailability, and no HPA-axis suppression was reported with single doses up to 4000 mcg, which is 20 times the recommended daily dose of 200 mcg (10). In studies comparing the *in vitro* effects of glucocorticoids in inhibiting cytokine production, histamine release and eosinophil survival, MF consistently ranked with fluticasone propionate as the most potent glucocorticoid, followed by beclomethasone, triamcinolone, budesonide, and betamethasone (11,12). MF was the most potent glucocorticoid analyzed *in vitro* for relative binding affinity for the glucocorticoid receptor and stimulation of receptor-mediated transactivation of gene expression (13).

MF has recently been formulated as a pure powder–lactose mixture (one part mometasone furoate to 5·8 parts lactose) for administration by a novel breath-actuated DPI for the treatment of asthma. The present study was the first clinical trial to evaluate MF DPI for the treatment of moderate asthma in patients who were previously maintained on inhaled glucocorticoids. This placebo-controlled study compared the efficacy and safety of twice-daily administration of three dosages of inhaled MF DPI (100 mcg, 200 mcg and 400 mcg) with MDI beclomethasone dipropionate (BDP; 168 mcg) in adults and adolescents.

Methods

PATIENTS

Male and female patients, 12 years of age or older, who had a history of asthma for at least 6 months and had been using an inhaled glucocorticoid daily for at least 30 days, were eligible to participate in the study. For the 2 weeks prior to the screening visit, the patients must have been on a stable regimen of flunisolide, triamcinolone acetonide (TAA), beclomethasone dipropionate (BDP), or fluticasone propionate (FP). All patients were non-smokers or had discontinued smoking more than 6 months prior to screening. Certain medications that might interfere with the action of inhaled corticosteroids (e.g. corticosteroids by other routes, bronchodilators, cromolyn sodium, antihistamines and decongestants) were restricted prior to the screening visit. At the screening visit, patients had to demonstrate reversibility of airway disease, which was defined as an increase in absolute forced expiratory volume in 1 s (FEV_1) of $\geq$12% (with an absolute increase of $\geq$200 ml) within 30 min after administration of two puffs of albuterol. Protocol inclusion criteria also required that patients demonstrate at screening and at baseline (day 1, prior to initiation of treatment) FEV_1 values $\geq$ 60% – $\leq$90% of predicted normal values. Before treatment assignments were unblinded, it was determined that two subjects included in this study did not meet this criterion (one with a FEV_1 of 101·6% and another with a FEV_1 of 99·6%). Therefore, these two subjects were not included in

the efficacy-evaluable data subset of subjects (see Statistical Analysis). In addition, subjects who had no follow-up data beyond the baseline visit, or who received dosing for no more than 2 days were also excluded from this data set. All patients had clinically acceptable values for complete blood count, blood chemistry profile, urinalysis, standard 12-lead electrocardiograms (ECGs) and vital signs, and all were free of other clinically significant disease. Patients screened at five sites were required to have a baseline unstimulated plasma cortisol level ≥ 5 mcg dl^{-1} and a level ≥ 18 mcg dl^{-1} 30 min after stimulation with cosyntropin (Cortrosyn®, Organon, Inc.), a synthetic form of adrenocorticotropic hormone (ACTH).

Patients were excluded for any of the following reasons: pre-menarche, pregnancy, or lactation; immunotherapy, unless on a stable maintenance; treatment with oral glucocorticoids for >14 days in the 6 months before screening, methotrexate, cyclosporin, or gold within 3 months, or systemic steroids or another investigational drug in the month before screening; dependence upon daily use of nebulized β-agonists; the need for ventilator support in previous 5 years; hospitalization for asthma in the previous 3 months; requirement of $>$ 12 puffs day^{-1} of albuterol on 2 consecutive days between the screening and baseline visits; an upper or lower respiratory tract infection (viral or bacterial) in the 2 weeks prior to screening; or evidence of clinically significant oropharyngeal candidiasis. Women of child-bearing potential were required to use an acceptable method of birth control.

STUDY DESIGN

This double-blind, randomized, double-dummy dose-ranging study compared three doses of MF DPI to placebo and BDP MDI and was conducted at 20 study centers in the U.S.A. Patients were randomized to one of the five treatment arms according to a computer-generated code. The protocol was approved by the institutional review board for each treatment centre, and written informed consent was obtained from each patient or from the parent or guardian of patients under 18 years of age. During a 1- to 2-week screening period, each patient continued the use of the previously prescribed inhaled glucocorticoid and was provided with an albuterol inhaler to be used as needed.

At the baseline visit, spirometry was performed to measure FEV_1, forced vital capacity (FVC), and forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25-75\%}$). Eligible patients discontinued the use of their previous inhaled glucocorticoid and were randomly assigned to one of the following treatments twice daily: MF DPI 100, 200, or 400 mcg; BDP MDI 168 mcg; or placebo. In keeping with the double-blind study design, each patient received both a DPI and an MDI inhalation device and was instructed to take one inhalation from the DPI followed by four inhalations from the MDI every morning and evening approximately 12 h apart.

All patients completed a daily diary card documenting morning and evening peak expiratory flow rate (PEFR), asthma symptoms, number of albuterol inhalations, number of nocturnal awakenings for asthma symptoms requiring albuterol use, adverse events and the use of study drug and concomitant medications. Treatment visits occurred after 1, 2, 4, 8, and 12 weeks of treatment. An oropharyngeal exam was performed at each visit, cultures taken if appropriate and evidence of candidiasis was recorded as an adverse event.

EFFICACY ASSESSMENTS

The primary efficacy variable was the mean change from baseline to endpoint (the last available treatment visit) in FEV_1. Secondary efficacy variables included mean changes from baseline in FVC, $FEF_{25-75\%}$, and PEFR; symptom scores; albuterol inhalation use; nocturnal awakenings due to asthma; and physician assessments of response to therapy. Severity of asthma symptoms (wheezing, difficulty breathing, and cough) was rated on a four-point scale (0 = none, 1 = noticeable, 2 = annoying, 3 = very uncomfortable). The physicians also rated wheezing on a four-point scale (0 = none, 1 = wheezing on forced expiration, 2 = wheezing during tidal volume on expiration only, and 3 = wheezing during tidal volume on expiration and inspiration). The response to therapy was numerically evaluated from 1 to 5, as much improved (1), improved (2), no change (3), worse (4), or much worse (5), when compared with symptoms at baseline.

Time to worsening of asthma was recorded and was defined as the first occurrence of any of the following: 20% or greater decrease in FEV_1 from baseline; clinical asthma exacerbation requiring emergency treatment, hospital admission, or treatment with asthma medications in addition to those permitted in the protocol; 25% or greater decrease on 2 consecutive days in AM or PM peak flow from the mean baseline AM value; more than 12 puffs per day for 2 consecutive days of use of a rescue bronchodilator (albuterol); or more than two treatments with nebulized albuterol on 2 consecutive days.

SAFETY ASSESSMENTS

HPA-axis function was assessed in patients from five of the 20 treatment centers. At the screening visit and again at week 12, plasma cortisol concentrations were determined in blood samples drawn at 0800 hours (± 1 h), before cosyntropin stimulation with an intravenous injection of 0·25 mg cosyntropin. Post-cosyntropin plasma cortisol concentrations were determined 30 min after the injection.

All patients were monitored for adverse events and changes in vital signs, hematological and blood chemistry profiles, and ECG during the 12-week double-blind treatment period. Concentrations of MF were measured in plasma samples collected on the last study day from the same patients who participated in cosyntropin stimulation tests before and 30 min after the last dose of MF, using a

validated high-pressure liquid chromatography (HPLC) assay with tandem mass spectrometry detection (14).

STATISTICAL ANALYSIS

With 60 subjects per treatment group there would be a 90% power (two-sided level of significance, $\alpha = 0{\cdot}05$) to detect a clinically meaningful difference in the mean change from baseline in FEV_1 between any paired treatment groups. This test would detect mean treatment differences of 11% or more from baseline. The evaluation of endpoint results adjusted for the discontinuation of patients over time by including the data from the last available treatment visit for each patient.

The change from baseline in FEV_1, as well as the secondary efficacy variables, were analysed using a two-way analysis of variance (ANOVA) that extracted sources of variation due to treatment and centre. Pairwise comparisons were based on least squares means from the ANOVA using a 5% significance level. If the test for non-decreasing response among the treatment groups was significant, each pairwise comparison was to be performed at the 0·05 (two-sided) level of significance, with no adjustment for multiple comparisons. Plasma cortisol concentration data from the cosyntropin stimulation tests were also analysed by the ANOVA model described above.

Responses for both the primary and secondary variable were analysed initially using the entire population of treated subjects so that efficacy conclusions were not biased by a subset analysis. Since a small percentage (4%) of patients were found to be non-evaluable, according to the criteria determined prior to unblinding the study, an efficacy-evaluable subset of patients was then used to confirm the results obtained for the primary efficacy variable. The results from this subset analysis supported the initial findings and showed that the data for these patients did not affect outcome.

Results

PATIENT POPULATION

A total of 365 subjects, 12–74 years old, were treated. Randomization resulted in comparable treatment groups at baseline with respect to demographics (Table 1) and asthma-related characteristics (Table 2). Mean FEV_1 at baseline was comparable among the treatment groups and ranged from 74 to 78% of predicted value. The majority of patients (76%) completed the study. The most common reasons for discontinuation were treatment failure (13%) and adverse events (6%), but their distribution among the groups was not comparable. Only 7 or 8% of patients treated with any dose of MF DPI or with BDP discontinued due to treatment failure, compared with 38% of placebo-treated patients. Adverse events resulted in discontinuation of 5, 3 and 4% for patients treated with MF DPI 100, 200 and 400 mcg b.i.d., respectively, 8% of those treated with BDP and 11% given placebo. The specific adverse events are described below.

EVALUATION OF EFFICACY: FEV_1

At endpoint, the differences in mean changes from baseline between each active treatment group and the placebo group were highly significant ($P < 0{\cdot}01$) for each objective efficacy variable (Table 3). A consistent trend towards greater improvement during treatment with MF DPI 200 mcg b.i.d. than with MF DPI 100 mcg b.i.d. was observed, with no apparent additional benefit with MF DPI 400 mcg b.i.d.

The mean change in FEV_1 from baseline, the primary efficacy variable, was significantly greater for each of the four active treatment groups than the placebo group ($P < 0{\cdot}01$) at endpoint (Table 3). The improvement in FEV_1 was sustained over time for all active treatment groups, and this effect was particularly evident for the MF DPI 200 mcg b.i.d. treatment group (Fig. 1).

TABLE 1. Patient demographics

	MF DPI			BDP	Placebo
	100 mcg b.i.d. ($n=76$)	200 mcg b.i.d. ($n=70$)	400 mcg b.i.d. ($n=74$)	168 mcg b.i.d. ($n=71$)	($n=74$)
Age (years)					
Mean (range)	38 (12–71)	36 (12–74)	37 (12–68)	37 (12–63)	37 (13–72)
Sex					
Female/Male	41/35	42/28	47/27	47/24	45/29
Race					
White/African American/Other	67/7/2	61/6/3	61/7/6	59/7/5	66/5/3
Body Weight (lb)					
Mean (range)	178 (94–317)	180 (95–320)	156 (69–313)	168 (102–261)	167 (82–335)
Smoking history					
Never/not in past 6 months	54/22	50/20	50/24	52/19	42/32

TABLE 2. Asthma-related baseline characteristics

	MF DPI			BDP	
	100 mcg b.i.d. ($n=76$)	200 mcg b.i.d. ($n=70$)	400 mcg b.i.d. ($n=74$)	168 mcg b.i.d. ($n=71$)	Placebo ($n=74$)
Duration of asthma (years)					
Mean (range)	21 (1–65)	18 (1–69)	16 (1–55)	18 (1–52)	18 (1–50)
FEV_1 predicted (%)					
Mean (range)	74 (60–91)	76 (56–102)	77 (59–95)	78 (60–100)	74 (60–91)
Mean absolute FEV_1 (l)	2·61	2·67	2·49	2·62	2·48
Mean AM PEFR (l min^{-1})	381	398	366	388	376
Inhaled glucocorticoid use					
BDP, mean mcg day^{-1} (n)	312 (25)	328 (30)	339 (29)	341 (22)	356 (27)
Flunisolide, mean mcg day^{-1} (n)	1130 (10)	1313 (8)	1000 (4)	1111 (9)	1063 (8)
FP, mean mcg day^{-1} (n)	435 (9)	363 (10)	440 (7)	550 (5)	388 (8)
TAA, mean mcg day^{-1} (n)	763 (32)	768 (22)	779 (34)	703 (35)	794 (31)
Theophylline use					
Yes/no	8/68	13/57	9/65	8/63	10/64

At endpoint, FEV_1 had decreased by a mean of 6·6% in the placebo group but had increased by 4·8, 7·1, and 6·2% in the MF DPI 100, 200, or 400 mcg b.i.d. groups, respectively, and by 3·0% in the BDP 168 mcg b.i.d. group. Despite the decreases in patient population over time and the disproportionate number of patients in the placebo group who discontinued due to treatment failure, the consistent improvement in FEV_1 for the MF DPI 200 mcg b.i.d. treatment group was significantly different from placebo at each treatment visit ($P \leq 0{\cdot}03$). The 400 mcg b.i.d. dose of MF DPI provided a significant response compared with placebo at most, but not all, treatment visits ($P \leq 0{\cdot}05$), with no apparent advantage over the 200-mcg b.i.d. dose. The mean changes from baseline in FEV_1 for the BDP 168 mcg b.i.d. treatment group were similar to those for the MF DPI 100 mcg b.i.d. treatment group. The difference in mean change in FEV_1 between the MF DPI 200 mcg b.i.d. and BDP 168 mcg b.i.d. groups was significant only at week 1 ($P=0{\cdot}04$).

Additional analyses evaluated the change in FEV_1 by severity of asthma in patients with a baseline FEV_1 <75% of the predicted value and those with a baseline FEV_1 ≥75% of the predicted value. In both subsets, the trends for improvement in FEV_1 were similar to those for the entire patient population (Table 3). In general, response to active drug treatment was more pronounced in patients with more severe asthma but there was little difference between the two subsets in the response to placebo (Table 3).

EVALUATION OF EFFICACY: OTHER MEASURES OF PULMONARY FUNCTION

Results of other assessments of pulmonary function supported the improvements in FEV_1 observed for the active treatment groups. The increase in FVC from baseline indicated that all doses of MF DPI were superior to placebo ($P<0{\cdot}01$) (Table 3). At endpoint, the increases in FVC of 4·7, 3·3, and 3·5% with MF DPI 100, 200, and 400 mcg b.i.d., respectively, and 2·0% with BDP 168 mcg b.i.d. were all significantly greater ($P<0{\cdot}01$) than the 4·7% decrease with placebo.

A more dramatic response was observed in the $FEF_{25-75\%}$, again supporting the FEV_1 data suggesting all active treatments were superior to placebo and that 200 mcg b.i.d. was the optimal dose of MF DPI (Table 3). At endpoint, the increase for MF DPI 200 mcg b.i.d. was significantly greater than that for MF DPI 100 mcg b.i.d. ($P=0{\cdot}05$), but there was no statistical difference between the 400 mcg b.i.d. dose of MF DPI and the 200 mcg b.i.d. dose ($P=0{\cdot}68$).

Mean values for PEFR, measured each day before dosing by the patient and before the use of albuterol (if required), increased from baseline values throughout the 12 weeks of treatment and these increases were higher in the morning than in the evening for all active treatment groups and the placebo group (Fig. 2). At endpoint, as at most treatment visits, the increases in morning and evening PEFR for each active treatment group (3·8–9·9%) were significantly greater ($P<0{\cdot}01$) than the decreases for the placebo group (−3·9 to −7·0%) (Table 3). Again, the analysis showed that MF DPI 200 mcg b.i.d., which provided significantly better control than the 100 mcg b.i.d. dose ($P<0{\cdot}02$), was the optimal dose for improvement in PEFR.

TIME TO WORSENING OF ASTHMA

Kaplan–Meier estimates of time to worsening of asthma showed that all four active treatments were different from placebo, which had a median time to worsening

of approximately 55 days (Fig. 3). Because more than 80% of patients in each active treatment group had not met criteria for worsening at their last visit, median time to worsening could not be determined for these groups. This measure of efficacy confirmed that all doses of MF DPI were superior to placebo and consistent with improved control of asthma.

EVALUATION OF ASTHMA SIGNS AND SYMPTOMS

Because patients' asthma was generally well controlled at study entry, relatively few patients reported symptoms or had symptoms at baseline. Therefore, results of symptom evaluation should be interpreted with caution. For those who did have symptoms, evening symptoms were less pronounced but qualitatively similar to morning symptoms. Mean scores were significantly lower for all active treatment groups than for placebo at most treatment visits ($P \leq 0{\cdot}05$, data not shown) and at endpoint ($P < 0{\cdot}01$, Table 3). Improvement of these symptoms was comparable among the MF DPI 200 and 400 mcg b.i.d. treatment groups and the BDP 168 mcg b.i.d. group and somewhat better than the improvement for the MF DPI 100 mcg b.i.d. treatment group.

Significant reductions in coughing for the active treatment groups compared to the placebo group were observed at endpoint ($P < 0{\cdot}01$, Table 3). There was little numerical difference among the three MF DPI groups in the reduction of coughing score, and no statistically significant differences were detected ($P > 0{\cdot}05$).

At baseline and throughout the 12 weeks of treatment, mean scores for the physicians' evaluation of wheezing were

TABLE 3. Summary of efficacy results (endpoint analysis)

	MF DPI			BDP	
	100 mcg b.i.d. ($n=76$)	200 mcg b.i.d. ($n=70$)	400 mcg b.i.d. ($n=74$)	168 mcg b.i.d. ($n=71$)	Placebo ($n=74$)
Pulmonary function					
FEV_1 (%)	4·8*	7·1%*	6·2%*	3·0%*	−6·6
FEV_1 (%) with FEV_1 < 75% predicted value at baseline	8·4	12·1	4·2	8·4	−7·9
FEV_1 (%) with $FEV_1 \geq$ 75% predicted value at baseline	0·4	2·6	7·5	0·2	−5·0
FVC (%)	4·7*	3·3*	3·5*	2·0*	−4·7
$FEF_{25-75\%}$ (%)	6·2*	18·8*	15·2*	7·5*	−9·5
AM PEFR (%)	4·6*	9·9*	9·3*	5·7*	−7·0
PM PEFR (%)	3·8*	9·3*	6·4*	3·1*	−3·9
Patient's self-reports					
AM wheezing scores	−0·15*	−0·22*	−0·25*	−0·25*	0·30
AM difficulty breathing scores	−0·15*	−0·31*	−0·25*	−0·29*	0·39
AM cough scores	−0·03*	−0·05*	−0·04*	−0·13*	0·36
Albuterol use per day (%)	22*	−21·4*	−2·3*	−21·4*	25·3
Number of nocturnal awakenings (n)	−0·02*	−0·08*	−0·12*	0·00*	0·31
*Physicians' evaluations					
Wheezing scores	0·00†	−0·14*	−0·00†	0·07	0·30
Response-to-therapy scores	2·38‡*	2·28‡*	2·33‡*	2·58‡*	3·56

*$P < 0{\cdot}01$ *vs.* placebo (change from baseline); †$P \leq 0{\cdot}05$ *vs.* placebo (change from baseline); ‡$P < 0{\cdot}01$ *vs.* placebo (absolute score).

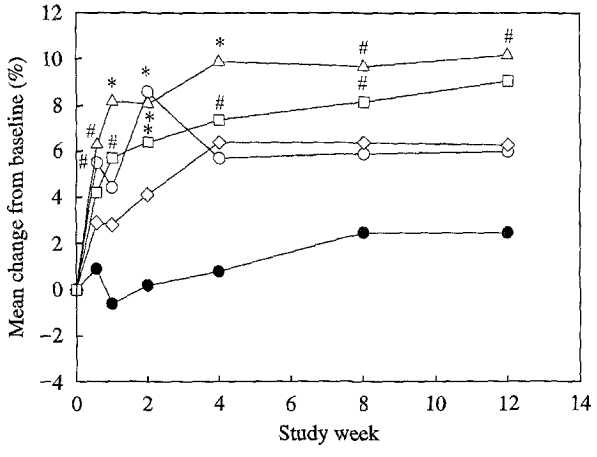

FIG. 1. Mean change from baseline in FEV_1. * $P < 0{\cdot}01$ *vs.* placebo; # $P < 0{\cdot}05$ *vs.* placebo. (MF DPI: ○, 100 mcg b.i.d.; △, 200 mcg b.i.d.; □, 400 mcg b.i.d.; BDP: ◇, 168 mcg b.i.d.; Placebo: ●.)

similar among the treatment groups, with few significant differences (data not shown). At endpoint, however, the scores for the three MF DPI treatment groups were significantly lower than that for the placebo group ($P \leq 0{\cdot}05$, Table 3); this difference was not observed for the BDP treatment group ($P > 0{\cdot}05$). The lowest mean score occurred in the MF DPI 200 mcg b.i.d. treatment group ($P < 0{\cdot}01$ *vs.* placebo).

RESCUE MEDICATION USE AND NOCTURNAL AWAKENINGS

Several other parameters were evaluated as additional measures of the efficacy of MF DPI (Table 3). Patients treated with MF DPI 200 or 400 mcg b.i.d. or BDP 168 mcg b.i.d. had the greatest decreases in rescue medication use. At endpoint, albuterol use had decreased by 21, 2, and 21% for the patients in these three groups, respectively, but increased by 25% for those in the placebo group ($P < 0{\cdot}01$).

Patients in all MF DPI treatment groups, but not the BDP treatment group, had fewer nocturnal awakenings requiring albuterol use than patients in the placebo group, with the greatest decreases observed with MF DPI 200 and 400 mcg b.i.d. versus placebo ($P < 0{\cdot}01$) at endpoint.

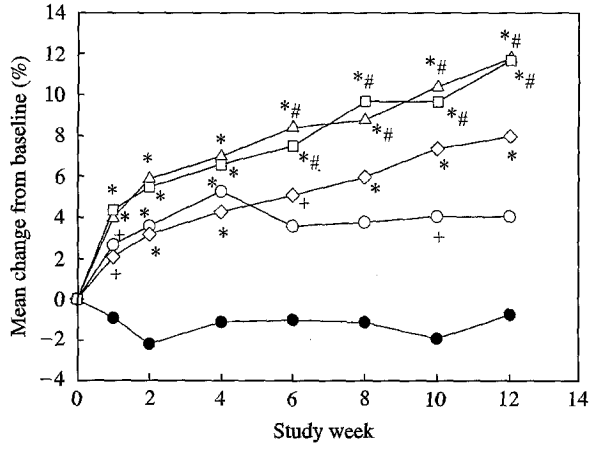

FIG. 2. Mean change from baseline in morning peak expiratory flow rate (AM PEFR). * $P < 0{\cdot}01$ *vs.* placebo; # $P \leq 0{\cdot}04$ *vs.* MF DPI: 100 mcg b.i.d.; $^{+}$ $P \leq 0{\cdot}04$ *vs.* placebo. (MF DPI ○, 100 mcg b.i.d.; △, 200 mcg b.i.d.; □, 400 mcg b.i.d.; BDP: ◇, 168 mcg b.i.d.; Placebo: ●.)

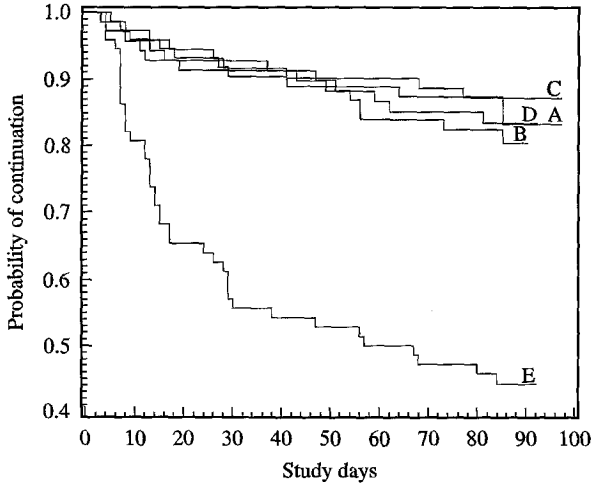

FIG. 3. Kaplan–Meier estimates of time to worsening of asthma (all treated subjects). (MF DPI: A, 100 mcg b.i.d.; B, 200 mcg b.i.d.; C, 400 mcg b.i.d.; BDP: D, 168 mcg b.i.d.; Placebo: E.)

PHYSICIANS' EVALUATION OF RESPONSE TO THERAPY

In the physicians' evaluation of the patients' response to therapy, numerical improvements were noted by day 4 for patients treated with MF DPI 200 ($P < 0{\cdot}01$) or 400 mcg ($P = 0{\cdot}05$) b.i.d. or BDP 168 mcg b.i.d. ($P = 0{\cdot}02$), but not until week 2 for those treated with MF DPI 100 mcg b.i.d. ($P = 0{\cdot}01$; data not shown). At endpoint, the symptoms in 67% and 66% of patients treated with MF DPI 200 and 400 mcg b.i.d., respectively, were improved or much improved, as compared with only 20% of those given placebo (Fig. 4).

Responses to MF DPI 100 mcg b.i.d. and BDP 168 mcg b.i.d. were comparable and also better than the response to placebo, with 56 and 51% of patients in the respective active treatment groups considered improved or much improved at endpoint. Similarly, symptoms in only 10–15% of patients in any of the four active treatment groups worsened, as compared with 57% of patients in the placebo group.

Statistical analysis confirmed the difference between the numerical scores for the placebo group and all active treatment groups ($P \leq 0{\cdot}02$), demonstrating a significantly better response by week 1 and at each subsequent treatment visit ($P < 0{\cdot}03$, data not shown). As observed with the assessments of pulmonary function and asthma symptoms, the greatest responses to therapy were seen in the MF DPI 200 and 400 mcg b.i.d. treatment groups, but there was no statistical evidence of an additional benefit of the higher dose of MF DPI.

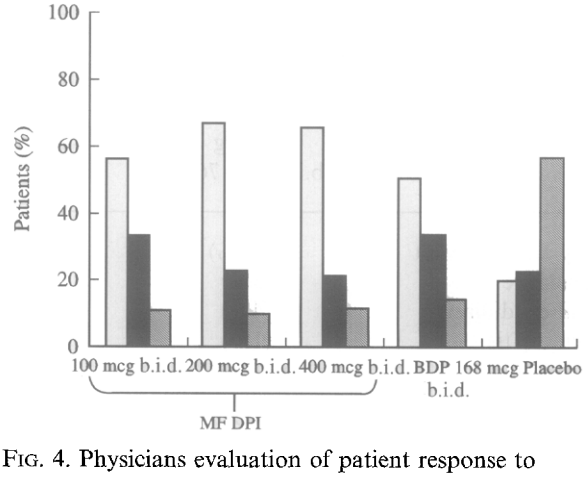

FIG. 4. Physicians evaluation of patient response to treatment at endpoint. (□, Improved or much improved; ■, no change; ▩, worse or much worse.)

EVALUATION OF SAFETY

Safety data showed that all doses of MF DPI were well tolerated. Treatment-related adverse events occurred in 18–28% of the patients in the MF DPI treatment groups, 21% of those in the BDP treatment group and 22% of patients in the placebo group (Table 4). The most frequently reported were headache, oral candidiasis and pharyngitis. Treatment-related headache was similar among groups (range: 3–5%). Oral candidiasis (4–15%) was reported more often for the MF DPI 400 mcg b.i.d. (15%) group than for the other dosage groups (1–6%). Most adverse events were mild to moderate in intensity and none was life-threatening. In only three patients was a treatment-related adverse event considered severe. These were aggravated asthma in one patient in the MF DPI 200 mcg b.i.d. treatment group and one in the BDP 168 mcg b.i.d. treatment group, and aggravated wheezing and chest pain in one patient in the placebo group.

Treatment with MF DPI or BDP was interrupted in some patients because of an adverse event, but generally these were considered unrelated to treatment and there was no pattern of occurrence. Of the 23 patients who discontinued treatment due to adverse events, only four had adverse events considered possibly or probably treatment-related (two patients in the placebo group and one each in the MF DPI 100 mcg b.i.d. and 400 mcg b.i.d. groups). No clinically relevant changes in vital signs, results of physical examinations, or median values for clinical laboratory tests were observed from baseline to endpoint for any treatment group.

COSYNTROPIN STIMULATION TEST RESULTS

The response to cosyntropin stimulation was analysed as the difference between post-stimulation and pre-stimulation plasma cortisol concentrations for 98 patients from five treatment centres, representing 18 or 20 patients from each treatment group. Mean pre-stimulation values for plasma cortisol were >5 mcg dl^{-1}, mean post-stimulation values were >18 mcg dl^{-1}, and mean changes from pre-stimulation to post-stimulation values were >7 mcg dl^{-1}. These results indicated no evidence of HPA-axis suppression in any treatment group.

There were no statistically significant differences among the treatment groups in mean pre-stimulation values, post-stimulation values, or the difference between them at either screening ($P \geq 0{\cdot}08$) or endpoint ($P > 0{\cdot}09$). Analysis of the mean change from screening to endpoint in the difference between post-stimulation and pre-stimulation values for plasma cortisol for each active treatment group was not significantly different from the change for the placebo group ($P \geq 0{\cdot}51$).

PLASMA CONCENTRATIONS OF MOMETASONE FUROATE

Mean plasma concentrations of MF were below or only slightly above the limit of quantification (50 pg ml^{-1}) immediately before and 30 min after the last dose, indicating minimal systemic exposure after oral inhalation for all MF treatment groups. No dose relationship was evident in the few patients who did have quantifiable plasma concentrations.

Discussion

The results of this 12-week dose-ranging study clearly demonstrate that mometasone furoate (100, 200 or 400 mcg) administered twice daily by breath-actuated dry powder inhaler was clinically superior in efficacy to placebo in adult and adolescent asthma patients being treated daily with inhaled glucocorticoids. MF DPI significantly improved all measures of pulmonary function, including the

TABLE 4. Incidence of frequently reported treatment-related adverse events (>2% of patients)*

	MF DPI			BDP	Placebo
	100 mcg b.i.d. ($n=76$)	200 mcg b.i.d. ($n=70$)	400 mcg b.i.d. ($n=74$)	168 mcg b.i.d. ($n=71$)	($n=74$)
Any adverse event	14 (18%)	18 (26%)	21 (28%)	15 (21%)	15 (22%)
Headache	2 (3%)	3 (4%)	3 (4%)	3 (4%)	4 (5%)
Oral candidiasis	3 (4%)	4 (6%)	11 (15%)	2 (3%)	1 (1%)
Pharyngitis	1 (1%)	7 (10%)	6 (8%)	3 (4%)	3 (4%)
Dysphonia	1 (1%)	1 (1%)	2 (3%)	1 (1%)	1 (1%)
Dyspepsia	0	2 (3%)	0	1 (1%)	0
Coughing	1 (1%)	0	0	0	2 (3%)
Dysmenorrhea	0	0	0	0	1 (2%)

*Considered by the investigators to be related, or probably related, to treatment.

primary efficacy variable, FEV_1, at all dose levels from baseline to the endpoint visit ($P<0{\cdot}01$) when compared with placebo. This effect was most consistent for the MF DPI 200 mcg b.i.d. treatment group. Patients treated with MF DPI also had significantly fewer signs and symptoms of asthma, less albuterol use as rescue medication and fewer nocturnal awakenings. In addition, the physicians' evaluation of response to therapy showed that all doses of MF DPI were more effective than placebo for clinical improvement from baseline.

The increases in FEV_1 in the MF DPI treatment groups were both statistically and clinically significant. All patients had been maintained on inhaled glucocorticoids prior to enrollment and switched to one of the active treatment groups at baseline. Therefore, the increases in FEV_1 indicated not only a continuation of the effect of previous inhaled glucocorticoid therapy but also an improvement over that effect. This observation was supported by the improvements in the FVC and parameters of lower airway function, including $FEF_{25-75\%}$, and morning and evening PEFR.

The results showed consistently that the 200 mcg b.i.d. dose of MF DPI was superior to the 100 mcg b.i.d. dose and that no additional benefit of the 400 mcg b.i.d. dose could be demonstrated. In addition, the efficacy of the MF DPI 100 mcg b.i.d. dose was similar to that of BDP 168 mcg b.i.d. This points to the sensitivity of the study design to demonstrate both the lower limit and the upper threshold of effective doses, since significant differences were found at endpoint in $FEF_{25-75\%}$ and PEFR with only a two-fold increase in dose, i.e. between the 100 and 200 mcg b.i.d. doses.

In contrast, dose-ranging studies of other inhaled glucocorticoids have failed to demonstrate significant differences in efficacy between adjacent dose levels, even with a four-fold or greater difference in dose (4). For example, three dose-ranging studies of fluticasone propionate, one comparing 25, 100 and 500 mcg b.i.d. and the other two comparing a narrower range of 50, 100 and 250 mcg b.i.d., show all doses more effective than placebo after 8 or 12 weeks of treatment, but no statistically significant differences among doses (15–17). Another study found a significant difference ($P<0{\cdot}05$) between daily doses of 100 and 200 mcg of fluticasone propionate in response to methacholine challenge, but not in endpoint values for pulmonary function tests, total symptom scores, or rescue bronchodilator use after 8 weeks of therapy (18). A crossover study comparing 400 and 1000 mcg BDP with 400 and 800 mcg BUD by aerosol inhalation failed to detect significant differences between the drugs or between the high or low doses of each drug (19).

However, several reports have suggested that higher than usual doses of inhaled glucocorticoid may lead to significant improvement in patients with moderate or severe asthma or those with stable disease (20,21). For example, Carpentiere *et al.* (20) found that higher doses of BDP (800 mcg b.i.d. *vs.* 100 mcg b.i.d. or 500 mcg b.i.d. *vs.* 250 mcg b.i.d.) led to greater improvement in FEV_1 and PEFR. In the present study, however, MF DPI 400 mcg b.i.d. provided no additional benefit over MF DPI 200 mcg b.i.d. for objective measures of pulmonary function and subjective assessments of response to therapy.

The cosyntropin stimulation test assesses the response of the adrenal glands to stimulation and, thus, of HPA-axis function (22). The present study found no evidence of clinically relevant HPA-axis suppression in any treatment group, as measured by response to cosyntropin stimulation. This lack of effect on cosyntropin stimulation of the HPA axis is consistent with studies with other inhaled glucocorticoids when employed at the low to mid range of clinically effective doses (4).

All doses of MF DPI were well tolerated in this study, with most adverse events of mild or moderate intensity. The most common treatment-related adverse events were headache, oral candidiasis, and pharyngitis. Although oral candidiasis occurred in 15% of the MF DPI 400 mcg b.i.d. group, no patients discontinued treatment due to this adverse effect. Candidiasis is reported at similar rates in other studies using inhaled glucocorticoids to replace oral glucocorticoids (23,24). Considering the lack of additional efficacy benefit with the 400 mcg b.i.d. dose in this study, these findings further suggest that MF DPI 200 mcg b.i.d. was the optimal dose in these patients with moderate persistent asthma being treated with inhaled glucocorticoids. It is possible that patients with severe persistent asthma may have a higher optimal dose.

In summary, this 12-week study showed that inhaled mometasone furoate administered by dry powder inhaler in a dose range of 100–400 mcg twice daily was significantly more effective than placebo for the treatment of moderate persistent asthma in adults and adolescents previously maintained on inhaled glucocorticoids. A dosage of 200 mcg twice daily provided significantly improved pulmonary function by the fourth day of treatment that was sustained for the duration of the study. This dosage also significantly reduced asthma symptoms, the need for rescue medication, and nocturnal awakenings due to asthma symptoms. MF DPI was also well tolerated, with no evidence of HPA-axis suppression.

References

1. National Institutes of Health. Clinical Practice Guidelines. Expert Panel Report 2. *Guidelines for the Diagnosis and Management of Asthma.* NIH Publication, No. 97–4051, 1997.
2. NHLBI/WHO workshop report. *Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention* Bethesda, MD: National Institutes of Health, National Heart, Lung and Blood Institute, 1995.
3. The British Thoracic Society, The National Asthma Campaign, Royal College of Physicians of London in association with the General Practitioner in Asthma Group, the British Association of Accident and Emergency Medicine, the British Paediatric Respiratory Society and the Royal College of Paediatrics and Child Health. The British guidelines on asthma

management 1995 review and position statement. *Thorax* 1997; **52:** S1–S21.
4. Pedersen S, O'Byrne P. Comparison of the efficacy and safety of inhaled corticosteroids in asthma. *Allergy* 1997; **52** (Suppl. 39):1–34.
5. Wilson AM, McFarlane LC, Lipworth BJ. Dose-response effect for adrenal suppresion with repeated twice daily inhaled fluticasone propionate and triamcinolone acetonide in adult asthmatics. *Am J Respir Crit Care Med* 1997; **156:** 1274–1277.
6. Hanania NA, Chapman KR, Kesten S. Adverse effects of inhaled corticosteroids. *Am J Med* 1995; **98:** 196–108.
7. Hebert JR, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 1996; **51:** 569–576.
8. Graft D, Aaronson D, Chervinsky P, *et al.* A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone aqueous nasal spray. *J Allergy Clin Immunol* 1996; **98:** 724–731.
9. Drouin M, Yang WH, Bertrand B, *et al.* Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for perennial allergic rhinitis patients. *Ann Allergy Asthma Immunol* 1996; **77:** 153–160.
10. Brannan MD, Seiberling M, Cutler DL, *et al.* Lack of systemic activity with intranasal mometasone furoate. *J Allergy Clin Immunol* 1996; **97:** 198 (abstract).
11. Umland SP, Nahrebne DK, Razac S, *et al.* The inhibitory effects of topically active glucocorticoids on IL-4, IL-5, and interferon-γ production by cultured pirmary CD4 T cells. *J Allergy Clin Immunol* 1997; **100:** 511–519.
12. Crocker IC, Church MK, Newton S, *et al.* Glucocorticoids inhibit proliferation and interleukin-4 and interleukin-5 secretion by aeroallergen-specific T-helper type 2 cell lines. *Ann Allergy Asthma Immunol* 1998; **80:** 509–516.
13. Smith CL, Kreutner W. In vitro glucocorticoid receptor binding and transcriptional activation by topically active glucocorticoids. *Arzneim-Forsch/Drug Res* 1998; **48:** 956–960.
14. Korfmacher WA, Bryant MS, Wardo CL, *et al.* Determination of mometasone furoate (SCH 32088) in human plasma via LC-APCIMS/MS. In: *Proceedings of the 33rd Eastern Analytical Symposium* 1994, Abstract 405.
15. Chervinsky P, van As A, Bronsky EA, *et al.* Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. *J Allergy Clin Immunol* 1994; **94:** 676–683.
16. Pearlman DS, Noonam MJ, Tashkin DP, *et al.* Compartive efficacy and safety of twice daily fluticasone propionate powder versus placebo in the treatment of moderate asthma. *Ann Allergy Asthma Immunol* 1997; **78:** 356–362.
17. Wasserman SI, Gross GN, Schoenwetter WF, *et al.* A 12-week dose-ranging study of fluticasone propionate powder in the treatment of asthma. *J Asthma* 1996; **33:** 265–274.
18. Noonan MJ, Chervinsky P, Wolfe J, Liddle R, Kellerman DJ, Crescenzi KL. Dose-related response to inhaled fluticasone propionate in patients with methacholine-induced bronchial hyperresponsiveness: a double-blind, placebo-controlled study. *J Asthma* 1998; **35:** 153–164.
19. Boe J, Rosenhall L, Alton M, *et al.* Comparison of dose-response effects of inhaled beclomethasone dipropionate and budesonide in the management of asthma. *Allergy* 1989; **44:** 349–355.
20. Carpentiere G, Marino S, Castello F, Baldanza C, Bonanno CT. Dose-related effect of beclomethasone dipropionate on airway responsiveness in asthma. *Respiration* 1990; **57:** 100–103.
21. Busse WW, Chervinsky P, Condemi J, Lumry WR, Petty TL, Rennard S, Townley RG. Budesonide delivered by Turbuhaler is effective in a dose-dependent fashion when used in the treatment of adult patients with chronic asthma. *J Allergy Clin Immunol* 1998; **101:** 457–463.
22. Feiss G, Morris R, Rom D, *et al.* A comparative study of the effects of intranasal triamcinolone acetonide aerosol (ITAA) and prednisone on adrenocortical function. *J Allergy Clin Immunol* 1992; **89:** 1151–1156.
23. Noonan M, Chervinski P, Busse WW, *et al.* Fluticasone propionate reduces oral prednisone use while it improves asthma control and quality of life. *Am J Respir Crit Care Med* 1995; **152:** 1467–1473.
24. Nelson HS, Bernstein IL, Fink J, *et al.* Oral glucocorticoid-sparing effect of budesonide administered by Turboinhaler. A double-blind, placebo-controlled study in adults with moderate-to-severe chronic asthma. *Chest* 1998; **113:** 1264–1271.